REMARKS

Claims 2, 5-7, 10, 15, 20, 25, and 30-34 are pending. Claims 2, 5, 10, 20, 25, and 30-34 are rejected under 35 U.S.C. § 112, first paragraph. Claims 2, 5-7, 10, 15, 20, 25, and 30-34 are rejected under 35 U.S.C. § 103. Claims 2, 5-7, 10, 15, 20, 25, and 30-34 are provisionally rejected on the ground on nonstatutory obviousness-type double patenting. Applicants address each basis for rejection as follows.

Amendment to the specification

The specification has been amended to recite the term "Z strain." As stated in Applicants' last reply, the Sendai virus "Z strain" is described in Figure 1 of Kato et al. (Genes Cells 1: 569-579, 1996; "Kato"), which is cited in the present specification (at page 27, lines 17-18, page 29, lines 14-15, 19-20, and 27-28, page 30, lines 12-13, and page 32, line 36, to page 33, line 1, of the English language specification). The specification states that "[a]ll publications cited herein are incorporated as a part of the specification" (page 44, lines 11-12).

In addition, all of the Sendai virus vectors used in Examples of the present specification are derived from Sendai virus Z strain. In particular, the present specification refers to "WO 00/70070" in the description of the Sendai virus vector construction (page 45, line 4, of the English language specification). WO 00/70070, in turn, refers to Kato as describing Sendai virus vector construction. As such, the Sendai virus vectors used in the Examples of the present specification clearly are derived from the Z strain. Applicants submit that this amendment does not introduce new matter.

Objection to the specification

The specification is objected to for an asserted lack of antecedent basis for the term "Z strain" recited in the claims. The specification has been amended to provide antecedent basis for the term "Z strain." This basis for objection may be withdrawn.

Rejection under 35 U.S.C. § 112, first paragraph

Claims 2, 5, 10, 20, 25, and 30-34 are rejected under 35 U.S.C. § 112, first paragraph for an asserted lack of written description in the specification as filed. The Office states (page 4; emphasis original):

> [I]t is noted that none of these cited pages teaches specifically the specific concept of using **a wild type Sendai virus vector of a Sendai virus Z strain without any heterologous transgene for producing a mature dendritic cell as encompassed by the instant claims**. The title of the instant application "Method of constructing transgenic dendritic cell", original claims and all the exemplifications do not support the concept of using a wild type Sendai virus strain Z for the production of a mature dendritic cell. Applicants are invited to point out the specific page and line numbers that support for such an embodiment.

In response, Applicants note that parts C and D of the Examples (at pages 48-51 of the English language specification) demonstrate that Sendai virus Z strain encoding only a marker gene (a GFP gene) has the ability to activate T cells and exhibits an anti-cancer effect. In this regard, the specification states that "[s]pecifically, when determined by the CTL assay, it was shown that dendritic cells were activated by SeV infection alone" (page 49, lines 21-22), and "[w]hen DC[dendritic cell]/SeV-GFP was used, significant anti-tumor effects could be observed" (page 50, lines 33-34).

Based on the above-described experimental results, the specification states (emphasis added):

> The minus-strand RNA viral vector may carry genes encoding one or more antigens or cytokines associated with diseases or may carry no foreign gene. Since the minus-strand RNA viral vector activates dendritic cells by infecting the cells, dendritic cells infected with the vector carrying no foreign gene can also activate patients' immune system. (page 42, lines 4-8)
>
> * * *
>
> Although the vector is expected to cause anti-tumor effect even if it does not carry a foreign gene, a stronger effect can be obtained by letting the vector carry an IFN-beta gene. (page 43, lines 11-13)

Applicants submit that the use of the wild-type Sendai virus Z strain, that is equal to the SeV-GFP vector from which the GFP gene is deleted, finds support in the specification as filed and that one skilled in the art would have recognized that Applicants were in possession of the presently claimed invention at the time of filing. The written description rejection of claims 2, 5, 10, 20, 25, and 30-34 may be withdrawn.

Rejection under 35 U.S.C. § 103

Claims 2, 5-7, 10, 15, 20, 25, and 30-34 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Song et al. (U.S. patent application publication no. 2002/0123479; "Song") in view of Tokusumi et al. (U.S. patent no. 6,746,860; "Tokusumi"), Jin et al. (Gene Therapy 10:272-277, 2003; "Jin"), Hwu et al. (U.S. patent no. 6,734,014; "Hwu"), and Waller et al. (U.S. patent application publication no. 2005/0013810; "Waller"). Applicants, for the reasons explained below, respectfully traverse this basis for rejection.

The Office states (page 5, last paragraph; emphasis original):

> Song et al disclose compositions and methods useful for stimulating an immune response against one or more disease associated antigens, including cancer associated antigens, by **genetically modifying dendritic cells including dendritic progenitor cells as well as dendritic cells having CD11c+ maker, *in vivo* or *ex vivo*, wherein the dendritic cells were genetically modified by a recombinant negative strand RNA virus (e.g., vesicular stomatitis virus, paramyxoviruses, orthomyxoviruses and bunyaviruses) directing the expression of at least one disease associated antigen** (see at least Summary of the Invention; particularly paragraphs 6-7, 9-12, 16-18, 41-45, 60 and Figure 1).

Song provides working examples using "retrovirus vectors" (paragraphs 0144-0260). Song further provides a working example for the construction of a plasmid encoding a Sindbis virus genome encoding an HBVe (hepatitis B virus) antigen sequence (paragraphs 0226 and 0227); however, there is no working example using a Sindbis virus vector. There is also no working example in Song using other vectors, for example,

minus-strand RNA virus vectors, such as paramyxovirus vectors, and, in particular, Sendai virus vectors. Therefore, the description of Song, relied on by the Office, regarding the use of paramyxovirus vectors is entirely *prophetic*.

Song also *prophetically* describes that viral vectors suitable for use in Song's invention include "vaccinia virus" (see paragraph 60), "herpes simplex virus" (see paragraphs 60, 87, and 120), and "Epstein-Barr virus" (see paragraphs 10, 40, 87, and 120). With regard to these other suitable virus vectors described by Song, Applicants provide the following summary of the state of the art at the time of filing.

State of the Art

As is evidenced by the following references, vaccinia virus, herpes simplex virus, and Epstein-Barr virus *inhibit maturation* of dendritic cells or *induce apoptosis* of dendritic cells.

Vaccinia virus

Engelmayer et al. (J. Immunol. 163: 6762-6768, 1999; "Engelmayer;" copy submitted with the December 6, 2010 Information Disclosure Statement) teach that "[v]accinia virus undergoes an abortive replication in both stages of DCs and *induces apoptotic cell death*" and "[f]urthermore, maturation of immature DCs and consequently T cell activation *are inhibited*" (see title and abstract of Engelmayer).

Herpes simplex virus

Salio et al. (Eur. J. Immunol. 29: 3245-3253, 1999; "Salio;" copy submitted with the December 6, 2010 Information Disclosure Statement) teach that "[u]sing a recombinant disabled infectious single cycle herpes simplex virus 1 (HSV-1) encoding green fluorescent protein, we show that the infected dendritic cells are defective in up-regulating costimulatory molecules, do not produce cytokines, and do not acquire

responsiveness to chemokines required for migration to secondary lymphoid organs" and that "[t]hese results reveal yet another strategy used by HSV-1 to evade the immune response, namely the *inhibition of signaling pathways involved in DC maturation*" (see title and abstract of Salio).

Epstein-Barr virus

Li et al. (Blood 99: 3725-3734, 2002, "Li;" copy submitted with the December 6, 2010 Information Disclosure Statement)) teach that "[h]ere we demonstrate that EBV infection of monocytes inhibits their development into dendritic cells (DCs), leading to an abnormal cellular response to granulocyte macrophage-colony-stimulating factor (GM-CSF) and interleukin-4 (IL-4) and to *apoptotic death*" (see title and abstract of Li).

As mentioned above, Song provides a mere prophetic description of the use of paramyxovirus. If a prophetic description were sufficient, Song's description of the use of vaccinia virus, herpes simplex virus, and Epstein-Barr virus, would also "teach" transducing dendritic cells with these viruses. However, as is evidenced by the above-cited references, vaccinia virus, herpes simplex virus, and Epstein-Barr virus *inhibit maturation* of dendritic cells or *induce apoptosis* of dendritic cells. These viruses cannot be used to produce a mature dendritic cell. Therefore any suggestion in Song that such viruses can be used is incorrect.

Applicants submit that, while prophetic examples described in prior art references may be eligible as prior art, these examples must be supported by a reasonable expectation of success. In the case of Song, however, the only experimental data provided use retroviral vectors. Song prophetically describes that vaccinia virus, herpes simplex virus, and Epstein-Barr virus can be used. In view of Engelmayer, Salio, and Li, which demonstrate that these viruses cannot be used, Song's prophetic teaching is incorrect. Applicants submit that the prophetic teachings in Song cannot be considered

prior art. Instead, the prior art, including Song, Engelmayer, Salio, and Li, if anything, suggests that the effect of a virus on dendritic cells is highly unpredictable, varying from virus to virus. Accordingly, Applicants submit that, contrary to the Office's assertion, Song does not teach the use of a "paramyxovirus" vector to produce a mature dendritic cell. To the extent the present obviousness rejection relies on Song as teaching the use of a paramyxovirus, this basis for rejection should be withdrawn.

The Office also states (pages 5-6 of the Office Action; emphasis original):

> Since the starting dendritic cells (including both dendritic cells and dendritic progenitors) used by Song et al do not express markers such as CD80, CD83 and CD86 (see at least Figure 1 for cellular dendritic cell markers taught by Song et al; paragraphs 9, 41-44), they fall within the scope of "immature dendritic cells" as defined by the present application (see at least page 10, lines 16-20; page 11, lines 14-19).

The Office raised this basis for rejection at page 11 of the Office Action issued on November 5, 2009. As stated in Applicants' April 28, 2010 response, Applicants maintain that the absence of information of whether a particular marker was expressed or not is not equivalent to a teaching that the marker was not expressed. In Figure 1 of Song, if the gene is not expressed in dendritic cells, it is clearly indicated by a "(-)" symbol, and Song states that "[m]arkers indicated with a (-) are not present on dendritic cells" (paragraph [0019], lines 2-3). Song is silent about whether CD80, CD83, or CD86 is expressed on dendritic cells. The Office's conclusion that Song teaches that CD80, CD83, and CD86 are not expressed on the cells used by Song does not follow from the data presented in Song. Song simply is silent on whether or not these markers are expressed.

For example, chemokine receptor 5 (CCR5) is not shown in Figure 1 of Song. If one were to follow the Office's proposed reasoning, one would conclude that the dendritic cell shown in Figure 1 of Song does not express CCR5. However, it was known in the art at the time that Song was published that immature dendritic cells express CCR5.

On this point Applicants direct the Office's attention to the abstract of Lin et al. (J. Exp. Med. 192(4): 587-594, 2000; copy submitted with an Information Disclosure Statement filed on January 10, 2012). The abstract reads as follows (emphasis added).

Abstract

Immature dendritic cells (iDCs) express the CC chemokine receptor (CCR)5, which promotes chemotaxis toward the CC chemokines regulated on activation, normal T cell expressed and secreted (RANTES), macrophage inflammatory protein (MIP)-1α, and MIP-1β. By contrast, mature DCs downregulate CCR5 but upregulate CXC chemokine receptor (CXCR)4, and as a result exhibit enhanced chemotaxis toward stromal cell–derived factor (SDF)-1α. CCR5 and CXCR4 also function as coreceptors for macrophage-tropic (M-tropic) and T cell–tropic (T-tropic) human immunodeficiency virus (HIV)-1, respectively. Here, we demonstrate chemotaxis of iDCs toward M-tropic (R5) but not T-tropic (X4) HIV-1. Furthermore, preexposure to M-tropic HIV-1 or its recombinant envelope protein prevents migration toward CCR5 ligands. The migration of iDCs toward M-tropic HIV-1 may enhance formation of DC–T cell syncytia, thus promoting viral production and destruction of both DC and T helper lymphocytes. Therefore, disturbance of DC chemotaxis by HIV-1 is likely to contribute to immunosuppression in primary infection and AIDS. In addition, migration of iDCs toward HIV-1 may aid the capture of R5 HIV-1 virions by the abundant DC cell surface protein DC-specific intercellular adhesion molecule (ICAM)3-grabbing nonintegrin (DC-SIGN). HIV-1 bound to DC cell–specific DC-SIGN retains the ability to infect replication-permissive T cells in trans for several days. Consequently, recruitment of DC by HIV-1 could combine with the ability of DC-SIGN to capture and transmit the virus to T cells, and so facilitate dissemination of virus within an infected individual.

Key words: dendritic cell • HIV • chemotaxis • chemokine • CCR5

Lin et al.

In accordance with the Office's reasoning, the dendritic cell shown in Figure 1 of Song does not express CCR5; and, based on the knowledge in the art, the dendritic cell shown in Figure 1 would therefore not be an immature dendritic cell. Applicants again submit that the lack of information about a marker gene does not mean that the marker gene is not expressed. Song fails to provide any indication whether or not CD80, CD83, or CD86 is expressed on dendritic cells.

Moreover, the dendritic cell shown in Figure 1 of Song is, more likely than not, a matured dendritic cell. CD54 and CD58 are maturation markers as shown in Figure 4 of Banchereau and Steinman (Nature 392:245-252, 1998; "Banchereau;" copy submitted with the Information Disclosure Statement filed on March 14, 2007). Dendrite formation

is also a hallmark of a matured dendritic cell. Two plus (++) expression of both CD54 and CD58 and numerous dendrites extended from the cell shown in Figure 1 of Song strongly suggest that the dendritic cell shown in Figure 1 of Song is a matured dendritic cell (see a matured dendritic cell shown in right hand of Fig. 4 of Banchereau) and not an immature dendritic cell as suggested by the Office.

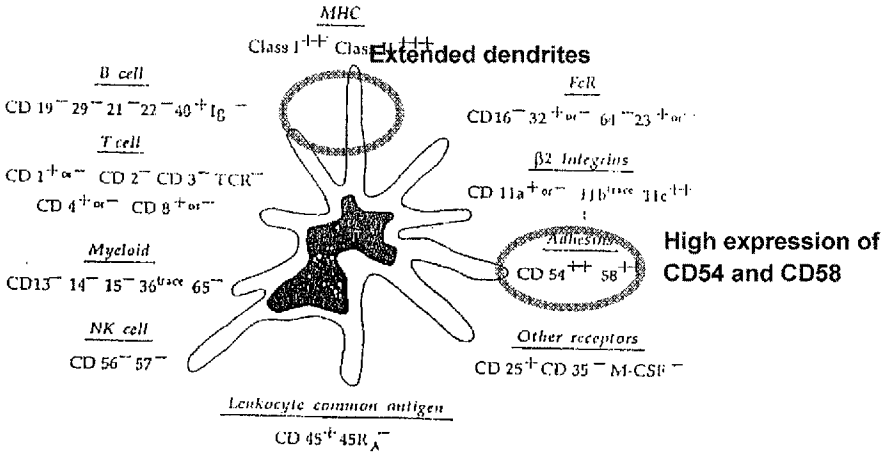

Figure 1 of Song (annotation and markings added)

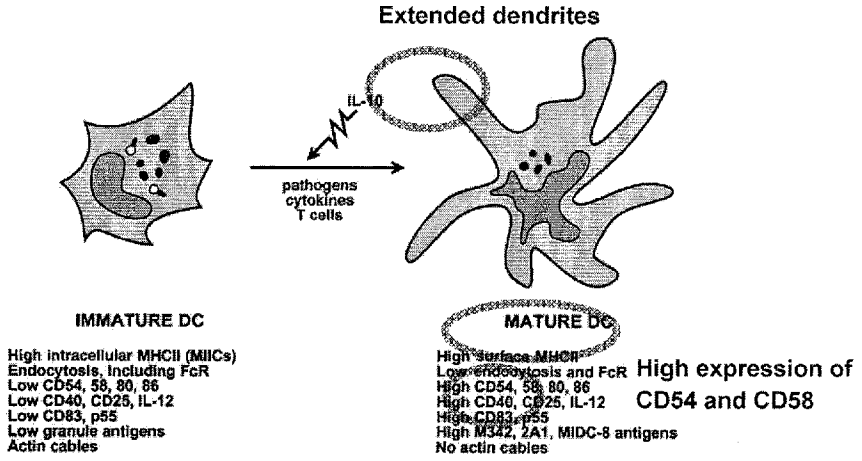

Figure 4 of Banchereau (annotation and markings added)

The Office further states (page 6, lines 5-7 of the Office Action):

> It is further noted that the transfected dendritic cells were not further subjected to any additionally treatment such as LPS stimulation for high expression of matured dendritic cell markers of CD80, CD83 and CD86.

Again, Applicants submit that a lack of information about stimulation does not mean the cells were not stimulated.

The Office goes on to state (page 6, lines 7-18 of the Office Action; emphasis original):

> **Song et al also disclose that it has been discovered that the efficiency of immune system stimulation mediated by genetically modifying dendritic cells can be several orders of magnitude greater than that mediated by genetically modified fibroblasts, muscle, and other cell types** (paragraph 39). Song et al further disclose that an expression vector may in addition to directing expression of at least one disease associated antigen, directs the expression of an immunomodulatory factor such as IL-12, IL-15, IL-2, beta-interferon among many others (paragraphs 68, 89-90). Song et al also teach that the genetically modifying dendritic cells, including allogeneic cells, are typically administered via parenteral or other traditional direct routes or directly into a specific tissue such as into the tumor in the case of cancer therapy in a mammal (e.g., a human) in need thereof (paragraphs 16-18, 43, 140, 164 and 176).

The cited description in Song is a general description of gene-modified dendritic cells and does not relate to dendritic cells introduced with Sendai virus. As such, Applicants submit that these statements are irrelevant in assessing the expectation of success of the claimed invention. As stated above, Song also describes that vaccinia virus, herpes simplex virus, and Epstein-Barr virus can be used to mature dendritic cells. However, in fact, these viruses are not useful for dendritic cell infection as evidenced by Engelmayer, Salio, and Li. Accordingly, Applicants submit that Song's description cannot be regarded as a teaching of what can be expected in using paramyxoviruses. This basis for the Office's obviousness rejection is not supported by the cited art.

In addition, at page 7, lines 4-14, the Office states (emphasis original):

> However, at the effective filing date of the present application, Tokusumi et al already disclosed the preparation of **at least a recombinant Sendai virus vector derived from a Sendai virus Z strain to be used for transfer of foreign genes** (see at least the abstract as well as Summary of the Invention; particularly example 1). Tokusumi et al also disclosed that **the Sendai**

virus vector is useful for gene therapy due to its safety, high gene transfer efficiency and capacity to express a foreign gene in a high level. Tokusumi et al further disclosed that **they have been focusing their attention on Sendai virus that is not pathogenic towards humans, particularly the Z strain that is especially avirulent; and a laboratory-attenuated Z strain has been isolated, widely used because of its safety and high production titers** (see at least col. 1, line 66 continues to line 31 of col. 2).

Tokusumi does not provide evidence that Sendai virus can be introduced into dendritic cells. Song states that vaccinia virus, herpes simplex virus, and Epstein-Barr virus can be used for gene transduction into dendritic cells, however these viruses cannot be used for this purpose as shown by Engelmayer, Salio, and Li. In view of the highly unpredictable nature of the introduction of virus vectors into dendritic cells, one of ordinary skill in the art would not have predicted that Sendai virus described in Tokusumi can successfully introduce a gene into dendritic cells with a reasonable expectation of success. Furthermore, Tokusumi does not teach the importance of using *immature* dendritic cells, a feature that is essential for efficient transduction of Sendai virus into dendritic cells.

The Office then goes on to state (pages 7-9 of the Office Action; emphasis original):

> Additionally, Jin et al already disclosed successfully a method in which recombinant Sendai virus was in contact and provided **a highly efficient gene transfer into human cord blood CD34+ cells,** including human cord blood HSCs and more immature cord blood progenitor cells (see at least the abstract; page 276, col. 1, last paragraph).
>
> Moreover, Hwu et al also taught at least a method of preparing **recombinant dendritic cells by transforming a hematopoietic stem cell, including CD34+ cells derived from a variety of sources such as cord blood, bone marrow and mobilized peripheral blood, with a nucleic acid followed by differentiation of the stem cell into dendritic cells in the presence of GM-CSF, TNF-alpha and optionally together with IL-4** (see at least the abstract; col. 9, lines 29-57; col. 10, line 60 continues to line 13 of col. 11; col. 15, lines 15-46).

Furthermore, Waller et al also taught that progenitors of dendritic cells or immature dendritic cells can be identified in many tissues, such as bone marrow and blood, based on the expression of certain cell surface markers; and that dendritic cell progenitors are typically identified by the expression of one or more of the following markers on its cell surface **CD11c,** CD13, CD14, CD33, **CD34** or CD4 (see at least paragraphs 24-28 and 36).

Accordingly, it would have been obvious and within the scope of skill for an ordinary skilled artisan to modify the teachings of Song et al. by also utilizing a recombinant Sendai virus vector derived from Sendai virus Z strain for genetically modifying immature dendritic cells, including CD11c+ and/or CD34+ dendritic precursor cells derived from bone marrow or cord blood to produce mature dendritic cells expressing at least a recombinant disease associated antigen as encompassed by the instant claims in light of the teachings of Tokusumi et al., Jin et al, Hwu et al and Waller et al as discussed above.

An ordinary skilled artisan would have been motivated to carry out the above modifications because Tokusumi et al already taught that the recombinant Sendai virus vector derived from a Sendai virus Z strain is useful for gene therapy due to its safety, high production titers, well characterized, high gene transfer efficiency and capacity to express a foreign gene in a high level. Additionally, a highly efficient gene transfer in human cord blood CD34+ cells which are dendritic precursor cells has been successfully achieved and demonstrated by Jin et al. Furthermore, dendritic cell progenitors typically identified at least by the expression of one or more of the following markers on its cell surface such as **CD11c or CD34,** derived from a variety of sources such as cord blood, bone marrow and mobilized peripheral blood, have been genetically modified for the preparation of mature dendritic cells expressing desired heterologous proteins/peptides as taught by Hwu et al and Waller et al.

The methods and compositions resulted from the combined teachings of Song et al., Tokusumi et al., Jin et al., Hwu et al and Waller et al are indistinguishable from the methods and compositions as claimed by the present application.

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of Song et al., Tokusumi et al., Jin et al., Hwu et al and Waller et al., coupled with a high level of skill for an ordinary skilled artisan in the relevant art.

> Accordingly, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Applicants submit that the Office has failed to establish a *prima facie* case of obviousness for the presently claimed invention. Hwu uses only retrovirus vector in Examples, which is akin to Song where, in the Examples, only retrovirus vectors are used for introduction to dendritic cells. As explained above, contrary to the description in Song, Engelmayer, Salio, and Li teach that various viruses such as vaccinia virus, herpes simplex virus, and Epstein-Barr virus inhibit maturation or induce apoptosis of dendritic cells. As such, successful introduction of a virus vector into dendritic cells was highly unpredictable at the time of filing, and, accordingly, prior to Applicants' findings, one of ordinary skill in the art would not have predicted that the Sendai virus Z strain used in Examples of Applicants' specification could be used to introduce a gene into CD11c+ immature dendritic cells, replicate its genome in the cells, and induce maturation of the dendritic cells with a reasonable expectation of success.

In response to Applicants' arguments presented in the last reply, the Office states (pages 9 and 10; emphasis original):

> Applicants' arguments related to the above modified rejection in the Amendment filed on 1/10/2011 (pages 6-9) have been fully considered but they are respectfully not found persuasive for the reasons discussed below.
>
> Applicants argue basically that none of the cited references describes the use of a vector of a Sendai virus Z strain; and that such a vector could be used successfully to produce mature dendritic cells. Applicants also argue that the Lopez et al reference (JID 187:1126-1136 2003) **which is not applied in the above 103 rejection**, already showed that Sendai Cantell virus is a potent inducer of IFN-I and Sendai 52 virus is a very poor inducer of IFN-I; and Lopez et al also concluded "[t]hese results establish a correlation between type I IFN production by DCs after viral infection and the induction of DC maturation". Based on the conclusion of Lopez et al, Applicants argue that the Sendai virus E72 used by Gary-Gouy et al (Journal of Interferons and Cytokines Research 22:653-659, 2002), **another reference not applied in the above 103 rejection**, which induced IFN-1 at

> very low level, is therefore also a poor inducer of DC maturation. As such, the prior art describes two Sendai virus strains, 52 and E72, which are poor inducers of DC maturation with only the Sendai virus Cantell was known to induce potent DC maturation. In contrast, Sendai virus Z strain of the present application is shown to be a potent inducer of DC maturation. Therefore, Applicants argue that nothing in the cited references would lead one skilled in the art to use a Sendai virus vector of a Sendai virus Z strain in a method for producing a mature DC, much less have a reasonable expectation that such a method would be successful. Applicants further argue that this is the unexpected result, supported by the examples of the application.

As an initial matter, Applicants note that it was the Office which cited and relied on Gary-Gouy in Office Actions issued on November 5, 2009 and July 22, 2010, and Lopez in the Office Action issued on July 22, 2010. In the present Office Action, the Office states that these references are "**not applied in the above 103 rejection**" using bold and underline. The references should, nonetheless, be considered in determining whether or not the presently claimed invention is obvious.

The Office also states (pages 10 and 11; emphasis original):

> First, Tokusumi et al disclosed explicitly the preparation of **at least a recombinant Sendai virus vector derived from a Sendai virus Z strain to be used for transfer of foreign genes** (see at least the abstract as well as Summary of the Invention; particularly example 1). Tokusumi et al further disclosed that **they have been focusing their attention on Sendai virus that is not pathogenic towards humans, particularly the Z strain that is especially avirulent; and a laboratory-attenuated Z strain has been isolated, widely used because of its safety and high production titers** (see at least col. 1, line 66 continues to line 31 of col. 2).

Various viruses such as vaccinia virus and herpes simplex virus were also well known as candidate gene transfer vectors. However, these viruses are not useful for dendritic cell transfection as evidenced by Engelmayer, Salio, and Li. Hence, Applicants submit that Tokusumi's description is not sufficient to provide a reasonable expectation of success in carrying out the presently claimed invention.

Further, the Office states (page 11; emphasis original):

> Second, the teachings of the Lopez et al reference are incompletely characterized by Applicants. Lopez et al stated "In summary, we have identified a strong correlation between the ability of a virus to trigger DC maturation and the induction of the type I IFN pathway. **Released type 1 IFN is not necessary for virus induced DC maturation and is not able to induce full maturation by itself** (figure 3). **The up-regulation of costimulatory molecules and MHC class II can be induced separately from the induction of cytokine release**" (page 1134, right col., second full paragraph). This summary and the data shown in the Lopez et al reference do not support Applicants' conclusion that Sendai virus strains, 52 and E72, are poor inducer of DC maturation while the Sendai virus Cantell strain is the only known potent inducer of DC maturation **simply based on the detectable level of induced secreted IFN-1**. Thus, there is no evidence that Sendai virus strain E72 is a poor inducer of DC maturation as argued by Applicants. It is clear however **all of the wild type Sendai virus strains 52, E72 and Cantell are capable of inducing DC maturation; including inactivated Sendai viruses (see at least Table 4 of the Lopez et al reference)**.

The Office, in reference to Lopez, states that "[r]eleased type 1 IFN is not necessary for virus induced DC maturation and is not able to induce full maturation by itself (figure 3)." Applicants do not disagree that Lopez shows that type I IFN itself is not necessary for dendritic cell maturation as shown in Table 3. Nonetheless, induction of type I IFN in dendritic cells caused by non-inactivated virus is still a sign for maturation of dendritic cells. Lopez, at page 1130, column 1, states that "secreted type I IFN is irrelevant for the induction of DC maturation by viruses" (emphasis added) because "MHC class II, costimulatory molecules, and cytokines were up-regulated normally after viral infection" even in the presence of anti-IFN antibody. However, even if the *secreted* type I IFN is irrelevant for maturation, Lopez states that "the induction of type I IFN secretion seems to correlate with DC maturation" (page 1134, col. 2, 1st full paragraph). Lopez further states that "[t]hese results establish a correlation between type I IFN production by DCs after viral infection and the induction of DC maturation" (page 1129, col. 1). Lopez

further states that "viruses that induce high levels of type I IFN are also better stimulators of DC maturation than those eliciting lower levels of IFN" (page 1134, col. 1, 1st paragraph; emphasis added). In view of these statements, Applicants submit that the Office's assertion is not supported by Lopez.

Applicants also submit that Lopez does not support the Office's assertion that "[i]t is clear however **all of the wild type Sendai virus strains 52, E72 and Cantell are capable of inducing DC maturation; including inactivated Sendai viruses (see at least Table 4 of the Lopez et al reference)**" (Office Action at page 11; emphasis original). It is true that a UV-inactivated Sendai virus induced the expression of maturation markers such as CD80 and CD86 as shown in Table 4 of Lopez. However, the virus used in Table 4 is "Sendai Cantell" which was the only Sendai virus known as a dendritic cell activator. The Office's assertion that Sendai virus strain 52 is also capable of inducing dendritic cell maturation is not supported by Table 4.

In fact, as seen in Figure 1 (reproduced below with annotation and arrows added), Lopez clearly shows that Sendai virus 52 cannot induce dendritic cell maturation.

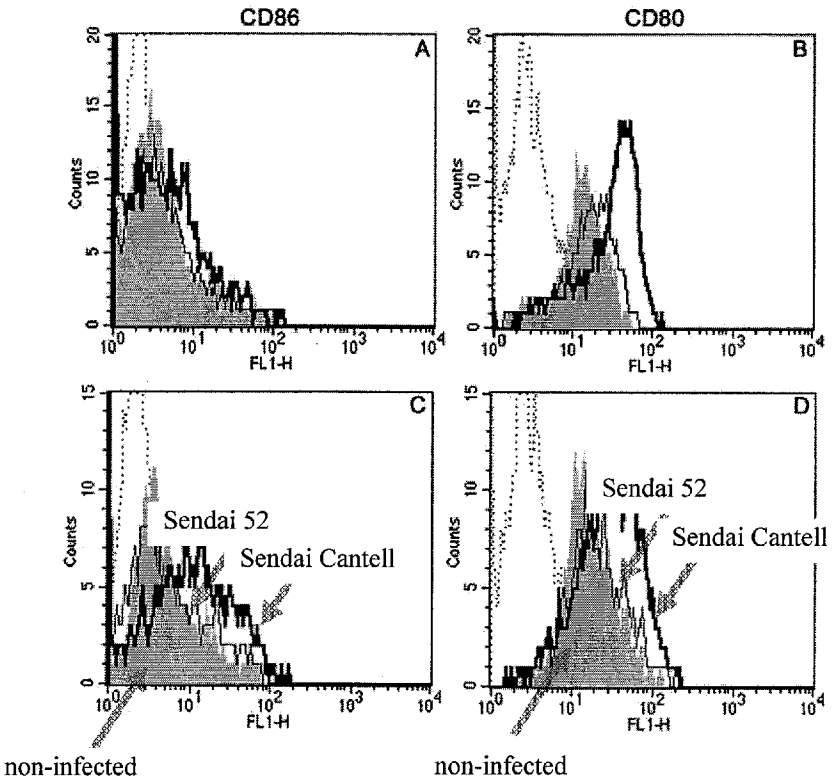

Figure 1 of Lopez shows the induction of maturation markers by two Sendai viruses. Panels C and D show that Sendai Cantell (thick line) elevated the expression level of maturation markers such as CD80 and CD86; however, Sendai 52 (thin line) did not elevate the expression level of these maturation markers. The non-infected control is shown as a filled graph. Therefore, Lopez provides clear evidence that Sendai 52 cannot induce maturation of dendritic cells. Accordingly, the Office's assertion is not supported by the data shown in Lopez.

Furthermore, Sendai virus Z strain not only induces maturation of dendritic cells, but also induces immuno-stimulatory cytokines such as IL-1β and TNF-α at high level as shown in Figure 18 of the present specification. No evidence is shown in Lopez that Sendai 52 induces these cytokines from dendritic cells.

The Office, at the top of page 12, states (emphasis original):

> Third, with respect to the above 103 rejection an ordinary skilled artisan would have been motivated to select specifically a recombinant Sendai virus vector of a Sendai virus strain Z over other strains because Tokusumi

> et al already taught clearly that **the recombinant Sendai virus vector derived from a Sendai virus Z strain is useful for gene therapy due to its safety, high production titers, well characterized, high gene transfer efficiency and capacity to express a foreign gene in a high level.**

Lopez states that "[f]or the Sendai viruses, the expression of the proteins F and HN was analyzed, and we observed >2 times higher expression of both proteins in cells infected with the lower IFN-inducing virus Sendai 52 (data not shown)" (page 1128, col., 2, 1st full paragraph). Namely, Sendai 52 expresses its F and HN proteins in dendritic cells higher than Sendai Cantell; nevertheless, Sendai 52 failed to induce maturation of dendritic cells as shown in Figure 1. Therefore, it simply does not follow that "high gene transfer efficiency and capacity to express a foreign gene in a high level" generally described in Tokusumi provides a reasonable expectation of success of induction of the dendritic cell maturation. Furthermore, induction of immuno-stimulatory cytokines as shown in Figure 18 of the present specification was also unpredictable.

The Office goes on to state (page 12; emphasis original):

> The spontaneous stimulation of immature dendritic cells to mature dendritic cells which are defined as dendritic cells having high expression of CD80, CD83 and CD86 is the "intrinsic property" of a selected Sendai virus. Therefore, this intrinsic property of a recombinant Sendai virus derived from strain Z would occur in the methods and compositions resulted from the combined teachings of Song et al., Tokusumi et al., Jin et al., Hwu et al and Waller et al as set forth in the above 103 rejection; regardless whether any of these inventors are aware of the degree or the extent of spontaneous DC maturation induced by Sendai virus strain Z. This is also an evidence that **the above 103 rejection was not** based on hindsight and/or reconstructed based on the specification of the present application.

The Office appears to suggest that any surprising effect of an invention may be ignored as an intrinsic property as long as the prior art references can be combined to include all of the claimed elements after having knowledge of the claimed invention. However, Applicants, at page 22 of the response filed on April 28, 2010, argued that such reasoning is improper and maintain that, even if the surprising effect is an intrinsic property of the

combination, the combination itself is not an intrinsic property of the prior art. The combination was made by the Office with knowledge of the presently claimed invention.

High expression of CD80, CD83, and CD86 is not an intrinsic property of solely the selected virus, because CD80, CD83, and CD86 are expressed not from the virus but from the genomic DNA of a $CD11c^+$ dendritic cell. High expression of CD80, CD83, and CD86 is the intrinsic property of the **combination of** a particular $CD11c^+$ immature dendritic cell **and** a particular Sendai virus strain. The combination encompassed by the claims did not exist before the present invention. The Office combines Song, Tokusumi, Jin, Hwu, and Waller, after having knowledge of the presently claimed invention, to make a combination which has the same elements as the claimed invention. The intrinsic property of the combination is different from an intrinsic property asserted by the Office to be present in the prior art.

Furthermore, Song, as explained above, does not describe the introduction of Sendai virus into immature dendritic cells (Figure 1 of Song does not show an immature dendritic cell). Therefore, the Office's combination of prior art does not teach or suggest all elements required by the claimed invention.

Finally, the Office states (pages 12 and 13):

> Fourth, at the effective filing date of the present application Li et al (J. Virol. 74:6564-6569, 2000; IDS) already demonstrated that **a Sendai virus vector mediated a gene transfer and expression in various types of animal and human cells, including non-dividing cells, with high efficiency; Steinman et al (US 6,300,090) also successfully transfecting** [*sic*] **proliferating or non-proliferating human dendritic cells (both mature and non-mature cells) with at least a recombinant influenza viral vector which is minus-strand RNA viral vector that belongs to the same family as Sendai virus vector (see at least issued claims of US 6,300,090); Kitazato et al (US 2003/0170266) also disclosed the use of F gene deficient Sendai virus, including strain Z for expressing therapeutc gene in dendritic cells (see at least the abstract; paragraphs 5-6 and 84).** Last, Curiel-Lewandrowski et al (J. Immunol. 163:174-183, 1999; IDS) also disclosed transfection of immature murine bone marrow-derived dendritic cells with a recombinant adenovirus to enhance the

effectiveness of an in vivo DC-based immunotherapy.

> Accordingly, there is nothing that is unpredictable or unexpected in transfecting dendritic cells (immature and/or mature dendritic cells) and/or dendritic cell precursors (CD34+ and/or CD11c+ cells) with a recombinant Sendai virus vector derived from strain Z at the effective filing date of the present application based on the combined teachings Song et al., Tokusumi et al., Jin et al., Hwu et al and Waller et al. coupled with the state of the relevant prior art as discussed above.

As stated above, Engelmayer, Salio, and Li teach that various viruses such as vaccinia virus, herpes simplex virus, and Epstein-Barr virus, which Song asserts can be used, instead inhibit maturation or induce apoptosis of dendritic cells. Furthermore, Lopez describes that "[f]or the Sendai viruses, the expression of the proteins F and HN was analyzed, and we observed >2 times higher expression of both proteins in cells infected with the lower IFN-inducing virus Sendai 52 (data not shown)" (page 1128, col., 2, 1st full paragraph). Namely, Sendai 52 expresses its F and HN proteins in dendritic cells higher than Sendai Cantell; nevertheless, Sendai 52 failed to induce maturation of dendritic cells. Therefore, Applicants submit that the cited references, including Li, Steinman, and Kitazato, do not provide a reasonable expectation of success for dendritic cell maturation using a Sendai virus Z strain. Further, none of the cited references teaches or suggests the significance of introducing Sendai virus vector into immature dendritic cells, which is essential for efficient introduction as shown in Fig. 9B of the present specification. Curiel-Lewandrowski is only tangentially related to the presently claimed invention as it merely describes adenovirus transfection.

In sum, in view of the highly unpredictable nature of the introduction of virus vectors into dendritic cells, none of the cited references, even if combined teach or suggest that a Sendai virus Z strain can successfully introduce a gene into dendritic cells with a reasonable expectation of success, much less the desirability of introducing the

vector into immature dendritic cells. The obviousness rejection over the cited art should be withdrawn.

Provisional Nonstatutory Obviousness-Type Double Patenting

Claims 2, 5-7, 10, 15, 20, 25, and 30-34 are provisionally rejected on the ground on nonstatutory obviousness-type double patenting over claims 2, 3, 7-9, 12, and 15-35 of co-pending application serial number 11/630,532 ("the '532 application").

Applicants again note that the present application, filed May 3, 2006, is the U.S. national stage of a PCT international application filed on October 29, 2004, whereas the '532 application, filed December 21, 2006, is the U.S. national stage of a PCT international application filed on April 28, 2005. Applicants submit that the present application, relative to the '532 application, is the earlier filed application. As such, in accordance with M.P.E.P. § 804, if the provisional obviousness-type double patenting rejection is the last remaining rejection in the present case, Applicants respectfully request that this provisional rejection be withdrawn and the application allowed to issue.

CONCLUSION

Applicants submit that the application is now in condition for allowance, and such action is hereby respectfully requested.

Enclosed is a Petition to extend the period for replying to the Office Action for three (3) months, to and including January 30, 2012, as January 29, 2012 falls on a Sunday.

Authorization is hereby provided to charge the extension fee required by 37 C.F.R. § 1.17(a), as well as any other fees or to apply any credits, to Deposit Account No. 03-2095.

Respectfully submitted,

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Jan N. Hittel, Ph.D.
Reg. No. 52,290

Clark & Elbing LLP
101 Federal Street
Boston, MA 02110
Telephone: 617-428-0200
Facsimile: 617-428-7045